Is nutrition important to postpone frailty?

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Abstract

Purpose of review: The purpose of the present study is to provide an updated, systematic review of the recent literature on whether nutrition is important to postpone frailty. **Recent findings:** A systematic review of recent literature (past 12 months) identified nine studies (eight of which using a cross-sectional design) exploring the relationship between nutrition and frailty. A single randomized-controlled double-blind trial was published. However, being a pilot study, it was characterized by a relatively small sample size, short follow-up length (i.e., 6 months), and low statistical power. Notably, available evidence shows considerable variability in participants' selection and assessment methods, rendering difficult direct comparisons. Size effects or magnitude of associations across the different studies cannot also be determined. **Summary:** There is a need for long-term, adequately powered, randomized controlled trials examining nutrition (alone or/and in combination with other appropriate interventions) as a means for postponing frailty in older persons.

Keywords: nutrition, frailty, review

Introduction

Frailty is a multidimensional syndrome characterized by decreased reserves and diminished resistance to stressors due to the cumulative declines of multiple physiological systems, and has been strongly associated with negative health outcomes (e.g., hospitalization, institutionalization, and death) in older persons [1, 2]. The frailty syndrome has attracted a significant and increasing scientific interest, because it is considered as a promising opportunity to quit the obsolete chronological criterion of age in the clinical decision process [3]. A number of factors have been thought to contribute to the aetiology of frailty, including genetic, epigenetic, chronic inflammation, morbidity, hormonal changes, and environmental factors (such as nutrition and physical activity) [1].

Several operational definitions of frailty are currently available in the literature [4]. However, the most commonly used operational definition is the one proposed by Fried *et al*., the so-called “frailty phenotype” [5]. It is based on the evaluation of five defining criteria: muscle weakness, slow gait speed, unintentional weight loss, exhaustion, and sedentary behavior. In parallel, a different model of frailty was proposed by Rockwood et al., the “frailty index” (FI) [6]. It is theoretically founded on the concept of frailty as the result of the arithmetical accumulation of deficits (i.e., clinical signs, symptoms, diseases, disabilities, psychosocial risk factors, and geriatric syndromes) occurring with aging. "Modified" versions of the frailty phenotype can be considered the Study of Osteoporotic Fractures (SOF) index (consisting of three items related to weight loss, subject’s inability to rise from a chair 5 times and reduced energy level) [7], and the Frailty Instrument for Primary Care of the Survey of Health, Ageing and Retirement in Europe (SHARE-FI, consisting of 5 items including fatigue, loss of appetite, functional difficulties, physical activity and physical weakness) [8].

A growing body of epidemiological evidence reports positive associations between individual nutrient intakes (e.g., vitamins D, C, E, protein and folate) [9-11], nutritional status (e.g.,

carotenoid, alpha-tocopherol, and 25-hydroxyvitamin D concentrations) [12, 13], healthier dietary patterns (e.g., the Mediterranean diet) [14-16] and frailty. Moreover, accumulating evidence suggests that nutrition represents an important and modifiable factor potentially affecting the frailty status of the older person [1]. Nutrition is not only involved in the direct assessment of frailty [4], but may also play a role in the definition of the interventions aimed at restoring robustness.

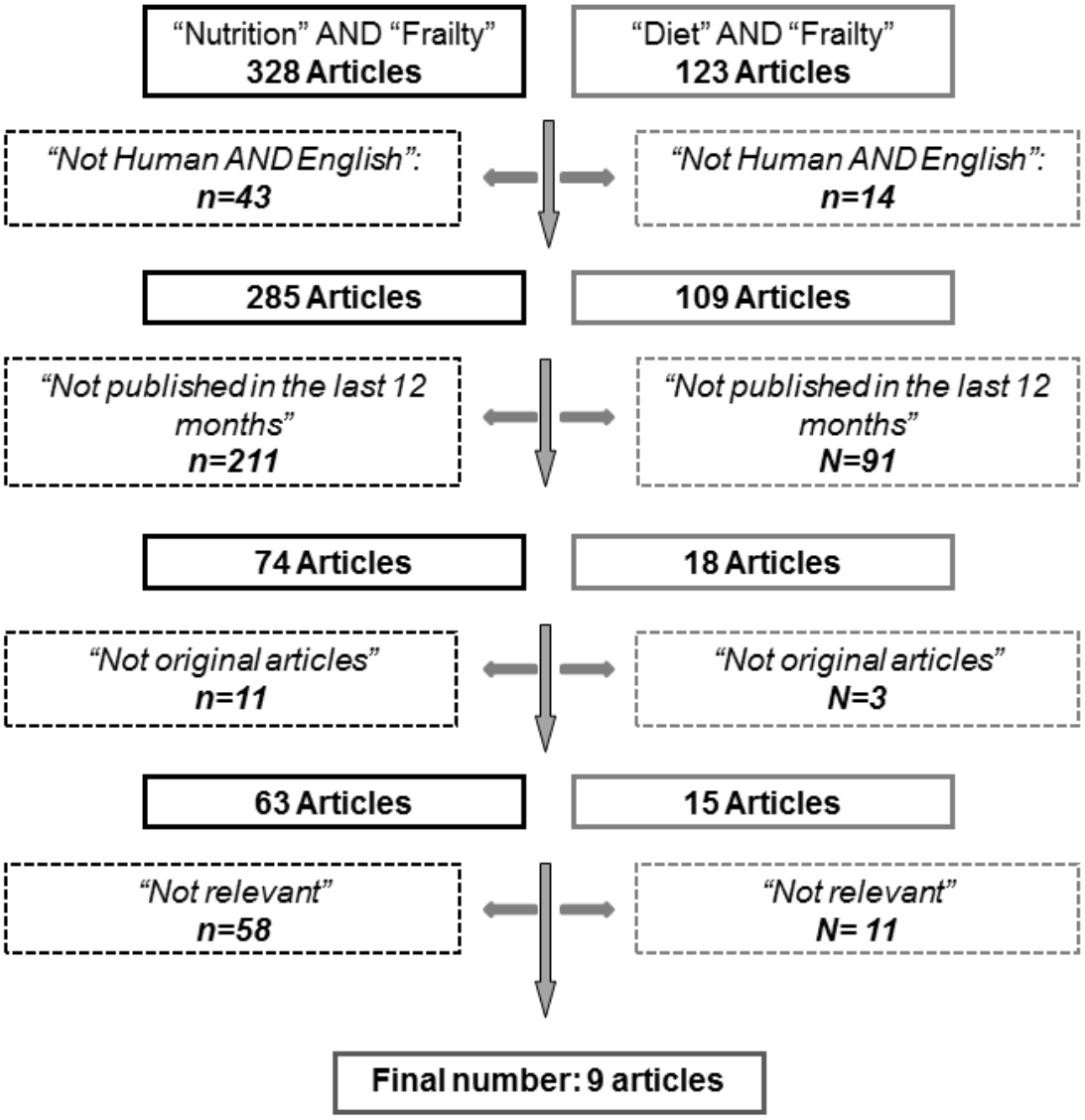
Given its capacity to provide beneficial effects on multiple systems and at biological, clinical, and social levels, nutrition may be considered as "multidomain" intervention *per se*. It is also noteworthy that nutritional interventions are characterized by great potentialities of being cost-effective, an issue of special importance when a large population is exposed to a specific risk (i.e., frailty) and needs to be (preventively) treated [17].

In the present review, we hypothesized that nutrition may have a positive impact on the frailty syndrome in older persons, potentially able to postpone the onset of its negative consequences. Therefore, the scope of the current work is to provide an up-to-date, review of the recent literature examining whether nutrition is important to counteract frailty.

Literature search

A Medline literature search of all articles published during the past 12 months was performed on the June 2, 2014 using the Medical Subject Heading (MeSH) terms "Human" and "English" combined with the terms 1) "Frailty" and "Nutrition", and 2) "Frailty" and "Diet" in PubMed (**Figure 1**). Overall, 92 articles were retrieved. The identified abstracts were evaluated for their relevance on the topic. The full articles were then obtained for the appropriate ones. A final selection of nine articles was used for the present review.

Figure 1. Flow chart of the retrieved and selected articles presenting results on the relationship between nutrition/diet and frailty.



Evidence from intervention trials and observational studies during the past 12 months

During the past 12 months, nine studies evaluated the relationship between nutrition and frailty (**Tables 1 and 2**). Only one randomized controlled trial was conducted. The study recruited 126 postmenopausal women aged 65 years and older [18]. Most of the participants were classified as pre-frail (according to the frailty phenotype) at baseline. Results showed that a 6-month supplementation with n-3 long chain polyunsaturated fatty acids was associated with a 3.0% increase of usual gait speed compared to the baseline value, whereas a reduction of this parameter (i.e., -3.5%, 0.03 m/sec) was observed in the control group. No significant difference was reported for the number of criteria defining the frailty phenotype between the two groups.

The available observational studies tend to show that intakes of total, animal, and plant proteins are inversely associated with frailty, especially in older women [19]. Moreover, higher adherence to a healthier dietary pattern (assessed using the Diet Quality Index-Revised) is both cross-sectionally and longitudinally associated with a lower risk of (incident) frailty in elders [16]. Frailty has also been associated with increased risk of malnutrition in homeless adults [20], as well as in community-dwelling [21], hospitalized [22], and institutionalized [23] older persons. It has been reported that pre-frail and frail individuals present a poorer nutritional status and higher food insufficiency in the Third National Health and Nutrition Examination Survey (NHANES III) [24]. Finally, another cross-sectional examination from the NHANES study documented an inverse relationship existing between urinary concentrations of O-desmethylangolensin (O-DMA; a metabolite of daidzein, an isoflavone) and frailty in women [25].

Table 1. Randomized controlled trials on frailty and nutrition published in the past 12 months

Randomized controlled double-blind pilot study	**Characteristics of participants**	**Setting**	**Definition of frailty**	**Intervention**	**Main results**
Hutchins-Wiese et al., 2013 [18*]	N=126 postmenopausal women (aged ≥65 years)	Community	Modified frailty phenotype	Intervention group (n=85): 2 fish oil capsules (1.2 g EPA and DHA) per day Control group (n=41): 2 olive oil capsules (1.8 g oleic acid) per day Follow-up: 6 months	No modifications of the frailty phenotype in the intervention or control groups at the end of the follow up Faster 8-foot walk walking speed (1.02±0.20 to 1.05±0.19 m/sec) in the intervention group compared to control group at the end of follow-up (p=0.038)

EPA: eicosapentaenoic acid; DHA: docosaexaenoic acid

Table 2. Observational studies on frailty and nutrition published in the past 12 months

Reference	**Characteristics of participants**	**Setting**	**Definition of frailty**	**Nutritional parameter**	**Main results**
Kobayashi et al., 2013 [19]	N=2108 Japanese women (aged 65-94 years)	Community	Modified frailty phenotype	Brief diet history questionnaire	Higher total, animal and plant protein intakes (≥84.3, ≥54.8, ≥33.9 g/d) were inversely associated with frailty (OR 0.65 [95%CI 0.46-0.91]; OR 0.73 [95%CI 0.50-1.06]; OR 0.66 [95% CI 0.45-0.95], respectively)
Shikany et al., 2013 (Cross-sectional & longitudinal analyses) [16]	N=5925 men (aged ≥65 years)	Community from the Osteoporotic Fractures in Men (MrOs) study	Modified frailty phenotype	Block 98 FFQ	The DQI-R was inversely associated with frailty status at baseline (OR for Q5 vs Q1 0.44 [95%CI 0.30-0.63]) and after 4.6 years of follow-up (OR for Q5 vs Q1 OR 0.44 [95%CI 0.30-0.63])
Smit et al., 2013 [24]	N=4731 men and	NHANES III non	Presence of ≥2 of	24-h dietary recall	Low daily energy intake in frail

	women (aged ≥60 years)	institutionalized population	the following 4 criteria: poor muscle strength, exhaustion, slow walking speed, sedentariness Presence of 1 criterion identifies prefrailty	Food insufficiency: self-report of 'sometimes'/'often' not having enough food to eat	(6648kJ) and prefrail (6966 kJ) individuals (P<0.01) Frail (adjusted OR 4.7 [95%CI 1.7-12.7]) and prefrail (adjusted OR 2.1 [95%CI 0.8-5.8]) persons were more likely to report food insufficiency than robust
Sánchez-García et al., 2014 [21]	N=1933 men and women (aged ≥60 years)	Community from the Study on Aging and Dementia in Mexico (SADEM)	Frailty phenotype	Body Mass Index Underweight/malnourished Overweight/obesity Normal weight	Frail (OR 1.49 [95%CI 1.41-1.58]) and prefrail (OR 1.89 [95%CI 1.81-1.97]) persons were more likely to be underweight or malnourished

Salem et al., 2013 [20]	N=150 men and women (aged 40-73 years)	Homeless adults from Los Angeles	Frailty Index (by Rockwood)	MNA	MNA score was inversely associated with FI (beta coefficient -0.17, SE 0.002; P<0.001)
Eichholzer et al., 2013 [25*]	N=600 women (aged ≥50 years)	NHANES 1999-2002 in non-institutionalized population	Modified frailty phenotype	Urinary phytoestrogen concentrations (isoflavones, lignans, daidzein, genistein, O-DMA, enterodiol, equol, equol among equol producers, enterolactone)	Reduced risk of frailty with increasing O-DMA urinary levels (OR 0.74 [95%CI 0.61-0.90])
El Zoghbi et al., 2014 [23]	N=111 men and women (aged ≥65 years)	3 long stay institutions in Beirut (Lebanon) of older adults with a MMSE score>14 points and without renal	SOF index	MNA	MNA score was inversely associated with the SOF index (beta coefficient -0.80 [95%CI -0.46, -0.13]; P=0.02)

		failure requiring dialysis			
Dorner et al., 2014 [22]	N=133 men and women (aged ≥65 years)	Hospitalized patients	SHARE-FI	MNA-Short Form	Cronbach's alpha=0.670 between MNA-Short Form and SHARE-FI, indicating a moderate overlap between frailty and poor nutritional status

FFQ: Food frequency questionnaire; DQI-R: Diet Quality Index Revised; NHANES: National Health and Nutrition Examination Survey; MNA: Mini Nutritional Assessment; O-DMA: O-desmethulangolensin; MMSE: Mini Mental State Examination score; SOF: Study of Osteoporotic Fractures; SHARE-FI: Frailty Instrument for Primary Care of the Survey of Health, Ageing and Retirement in Europe

Discussion

Our review of recent literature has allowed the identification of a very limited number of studies aimed at exploring the relationship between nutrition and frailty in the elderly. Moreover, available evidence is characterized by an overall heterogeneity in terms of objectives and methods.

Eight out of the nine selected studies reported results from cross-sectional analyses. The majority of these articles assessed frailty using the criteria proposed by Fried *et al*. Among the available observational studies, frailty was inversely associated with protein intake (from both plant and animal origins) [19], and urinary phytoestrogen concentrations [25], and positively associated with food insufficiency [24]. Moreover, a better quality of diet was both cross-sectionally and longitudinally associated with lower risk of being frail [16]. A strong and consistent relationship between frailty and malnutrition was reported in different healthcare settings and populations [22, 23, 20, 21].

Notably, we identified only one randomized controlled trial published in the past 12 months specifically aimed at evaluating the effects of a nutritional intervention (i.e., fish oil supplementation) on physical performance and frailty [18]. Nevertheless, the study was primarily aimed at exploring the effects of the nutritional intervention on bone turnover markers. Moreover, due to its pilot nature, the trial was characterized by a relatively small sample size, a short follow-up duration, and was not adequately powered to draw definitive conclusions on frailty. It is also noteworthy that the control group received olive oil capsules. Therefore, it cannot be excluded that the negative results could not be explained by some beneficial effects that olive oil constituents may have on physical performance [26], thus reducing the effect size of the intervention on the frailty phenotype.

A major limitation of the retrieved evidence consists in the multiple and different methods used to assess both frailty as well as nutrition. The heterogeneity of the studied populations

(i.e., hospitalized, institutionalized, homeless or community-dwelling older adults) may also complicate the conduction of direct comparisons and challenge the interpretation of results.

Conclusions

During the past year, there have been a limited number of studies investigating the association between nutrition and frailty. Although, the present review contributes towards the ongoing research in the emerging field of frailty, firm conclusions about the efficacy of nutrition on frailty cannot still be definitively drawn. Current evidence seems indeed inadequate to clearly address whether nutrition may postpone frailty. Such uncertainty is largely attributed to the cross-sectional nature of most of the available studies and the heterogeneity of available evidence. Our review clearly indicates the need of designing and developing *ad hoc* randomized controlled trials investigating such an important issue for geriatric medicine and public health systems.

Key-points

- Nutrition is an important aspect with the potential of reversing frailty in the elderly.
- Relatively few studies have been published during the past 12 months on the associations between nutrition and frailty (mainly cross-sectional observations).
- Further studies specifically designed for exploring the importance of nutrition to postpone frailty are needed.

Conflicts of Interest

Dr Matteo Cesari has received a research grant from Pfizer, and been serving as consultant for Nestlé, Novartis, and Pfizer.

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